IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Dales
Serial No:	08/732,479
For:	Preparation of Purines
Art Unit No.:	1611
Examiner:	Mark L Berch

DECLARATION OF GRAHAM RICHARD GEEN

I, Graham Richard Geen, hereby declare:

1. That I am Graham Richard Geen of SmithKline Beecham p.l.c., New Frontiers Science Park, Harlow, Essex, CM19 5AW, United Kingdom. I was awarded an honours degree of Bachelor of Science (Chemistry) in 1973 and the degree of Doctor of Philosophy in 1979, both from the University of Bristol. Since 1979 I have been employed by Beecham Group p.l.c. and SmithKline Beecham p.l.c. in various capacities relating to medicinal and synthetic chemistry, having spent 14 years working in the antiviral field. At the present time, I am an Assistant Director in the Department of Synthetic Chemistry. I am responsible for the work of 7 graduate chemists. I am an author or co-author of over 25 scientific publications and presentations.

2. I am familiar with the present application US Serial No. 08/732,479 ('479), which relates to a process for the production of purines, e.g. famciclovir and penciclovir. I am also familiar with European Patent Application No. 302644 ('664) filed 25 July 1988, for which I am named as joint inventor.

3. '644 discloses a process for the production of purines of formula (A) using as starting materials a purine derivative of formula (II), e.g. 2-amino-6-chloropurine (ACP), and a tricarboxylate of formula (V). The desired compound of formula (A) does not contain a 6-chloro substituent, but a hydrogen. The process shown in '644 uses ACP as a starting material, but does not indicate when the chlorine should be removed to yield the desired dechlorinated final product of Formula (A). The only guidance regarding removal of the 6-chloro substituent in the '644 application is provided for in the

exemplified production of famciclovir. This process uses the following sequence of reactions, see Annex 1:

a) coupling of triethyl 3-bromopropane-1,1,1-tricarboxylate (formula (V)) to 2-amino-6-chloropurine (formula (II)) (Description 11);
b) removal of the 6-chloro substituent (R_2) (Description 12);
c) decarboxylation (Example 3);
d) reduction (Step A(b)); and
e) *O*-acetylation (Step A(c)).

4. The coupling step a) of '644 produces not only the desired N-9 isomer (Compound 1, Annex 2) and the unwanted N-7 isomer (Compound 2, Annex 2), but also smaller amounts of the corresponding N-9 and N-7 diesters (Compounds 3 and 4, Annex 2) which result from *in situ* decarboxylation. The process of '644 is inconvenient for use on a large, commercial scale, because it requires chromatographic separation of the desired N-9 isomer and unwanted N-7 isomer. In addition to suppressing the yield of the desired N-9 isomer (Compound 1, Annex 2, the presence of the N-9 and N-7 diesters (Compounds 3 and 4, Annex 2) further complicates the isolation of the N-9 isomer since 4 products are present in the reaction mixture. Hence in Description 11 the isolation procedure for Compound 1, Annex 2, involves numerous steps, viz:

i) removal of N,N-dimethylformamide;
ii) addition of ethyl acetate, washing and drying;
iii) removal of ethyl acetate;
iv) recrystallisation from butan-1-ol;
v) evaporation of butan-1-ol from filtrate;
vi) column chromatography of filtrate residue; and
vii) evaporation of eluant.

5. The process of '479, which was invented during attempts to facilitate large scale commercial production of purines of formula (A), uses the following sequence of reactions, see Annex 3:

a) coupling of compound of formula (V) with a compound of formula (II) to yield a compound of Formula (VI) (Example 1);
b) decarboxylation (Example 1) (to give Compound 5, Annex 3);
c) reduction (Example 2);
d) *O*-acetylation (Example 2); and
e) removal of the 6-chloro substituent (R_2) (Example 3).

Notably, in this process the 6-chloro substituent remains in place until the final step of the synthesis instead of being removed after the coupling step a) as in '644.

6. In the process of '479 the triethyl ester (VI) is converted without isolation to the dimethyl ester, Formula (I), this N-9 isomer is then selectively precipitated from solution, free of the unwanted N-7 isomer. The process of '479 thus avoids the problems encountered in '644 since the presence of the 6-chloro substituent

allows the N-9 isomer to be selectively precipitated from the N-7 isomer, and decarboxylation of the entire reaction mixture reduces the number of products from 4 to 2. The advantage offered by this process is illustrated by the fact that the coupling and decarboxylation steps of the '479 process give an overall yield of 65% whereas the decarboxylation step alone of '644 only gives a yield of 59%.

7. In the process of '479 the yield at each step, and the overall yield, is substantially improved compared with that obtained using the process of '644. The overall yield of the '479 process is 41% and the overall yield of '644 process is 10.6%. The improved yields of the present invention arise through the maintained presence of the 6-chloro substituent until the end of the synthesis.

8. A further advantage of the process of '479 is found in the reduction step, paragraph 5 (c) above, where the reaction mixture is worked up using an aqueous solvent. In this step, it was found that the 6-chlorodiol is in fact less soluble than the dechlorinated diol, thus allowing easy isolation of the acetylated intermediate of the '479 process (see Example 2). This advantage is illustrated by the fact that the reduction and *O*-acetylation steps of the '479 process give a yield of 70% whereas the reduction and *O*-acetylation steps of the '644 process give a yield of 50.5% x 67% = 33.8%.

9. To summarize, the continued presence of the 6-chloro substituent during decarboxylation and through to the final step of the process is particularly advantageous because it allows:

a) convenient separation of the N-9 and N-7 isomers without requiring chromatography; and

b) the presence of the 6-chloro substituent in the diol produced in the reduction step decreases the solubility of the diol allowing convenient isolation in an aqueous solvent.

These advantages could not have been predicted from the disclosure of '644.

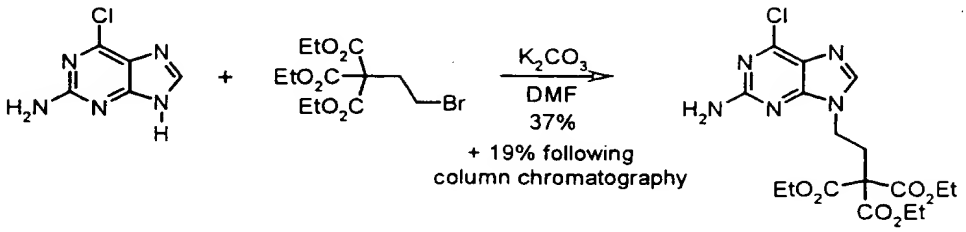
10. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of this application or any patent issuing thereon.

Date: _____ _____

Annex 1

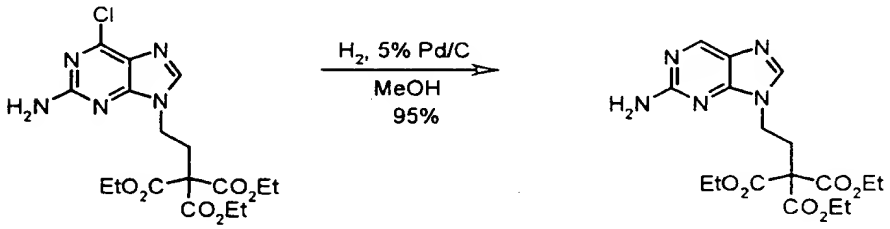
PROCESS FOR THE PREPARATION OF FAMVIR DISCLOSED IN EP 0 302 644 B1

Description 11

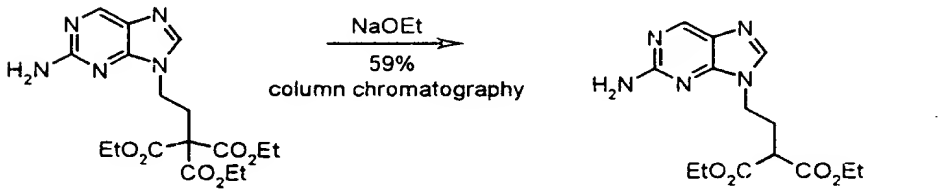


(reaction produces N-9 and N-7 triesters, plus smaller amounts of corresponding diesters)

Description 12

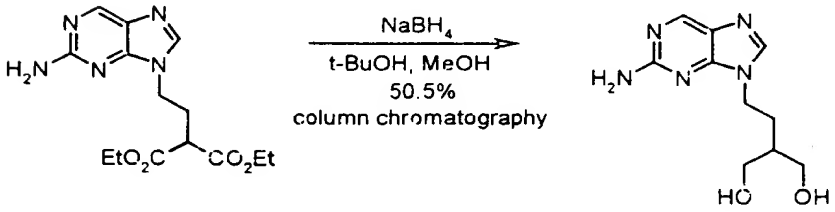


Example 3

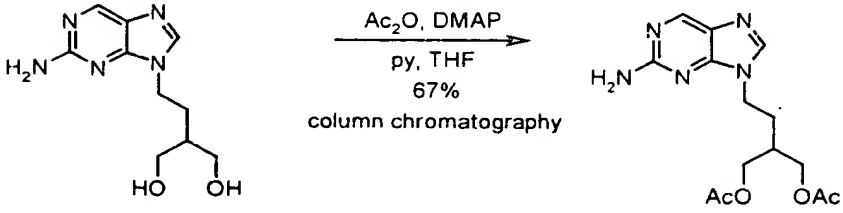


corresponding dimethyl ester is an oil
(see Example 1)

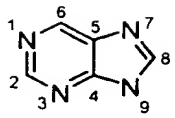
Preparation b) p.14

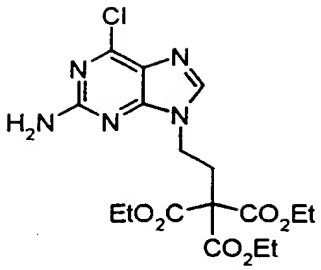


Preparation c) p.14

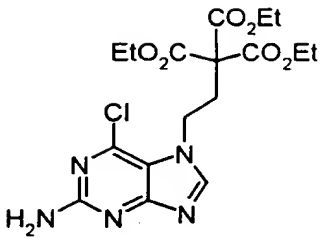


ANNEX 2





COMPOUND 1



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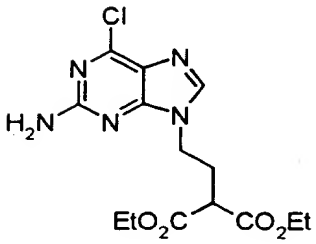
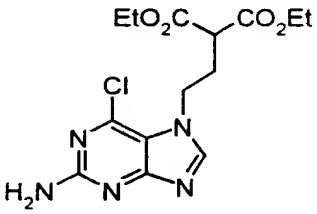


COMPOUND 3

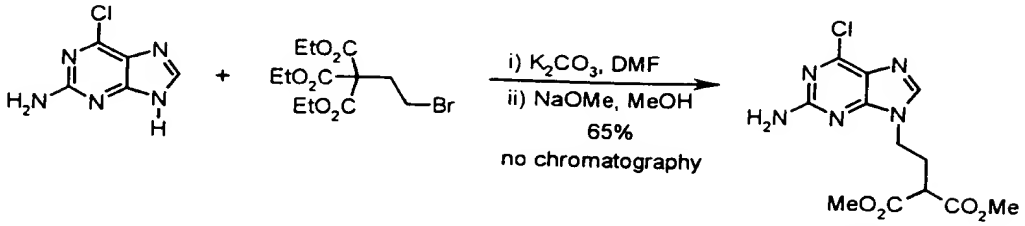


COMPOUND 4

ANNEX 3

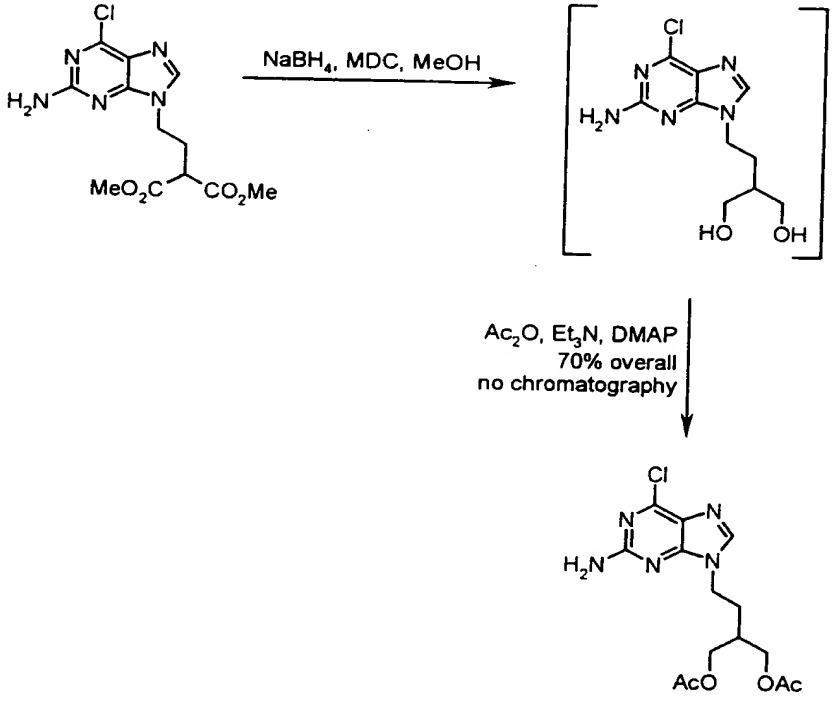
PROCESS FOR THE PRODUCTION OF FAMCICLOVIR DISCLOSED IN USSN 08/732,479

Example 1



COMPOUND 5

Example 2



Example 3a